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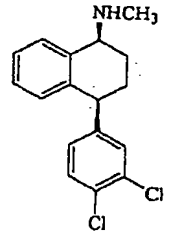
(54)【発明の名称】　塩酸セルトラリンの製法

(57)【要約】
【課題】従来の安定した結晶構造を有する塩酸セルトラリン（Form I）とは異なり、各種溶媒に対する溶解性やバイオアベイラビリティが良好であると考えられている準安定形の結晶構造を有する塩酸セルトラリンの製法を提供すること。
【解決手段】セルトラリン遊離塩基を溶媒に溶解させるか、またはセルトラリン有機酸塩を溶媒に懸濁させた後、得られた溶液または懸濁液に塩酸または塩化水素を導入することを特徴とする式（Ｉ）：
【化１】



・ HCl　　(Ｉ)

で表される準安定形塩酸セルトラリン結晶の製法。

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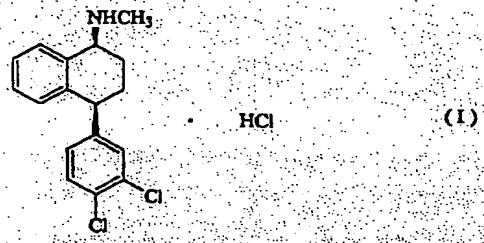
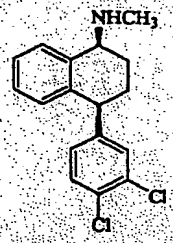
【特許請求の範囲】
【請求項1】　セルトラリン遊離塩基を溶媒に溶解させるか、またはセルトラリン有機酸塩を溶媒に懸濁させた後、得られた溶液または懸濁液に塩酸または塩化水素を導入することを特徴とする式（Ｉ）：
【化1】



・　HCl　　（I）

で表される準安定形塩酸セルトラリン結晶の製法。
【請求項2】　溶媒が、エステル系有機溶媒、ケトン系有機溶媒またはそれらの混合溶媒である請求項1記載の準安定形塩酸セルトラリン結晶の製法。
【請求項3】　溶液または懸濁液に塩酸または塩化水素を導入する際の温度が、室温～溶媒の還流温度である請求項1または2記載の準安定形塩酸セルトラリン結晶の製法。
【発明の詳細な説明】
【0001】
【発明の属する技術分野】本発明は、準安定形塩酸セルトラリン結晶の製法に関する。さらに詳しくは、抗うつ剤などとして有用な（1S，4S）－4－（3，4－ジクロロフェニル）－1，2，3，4－テトラヒドロ－N－メチル－1－ナフチルアミン塩酸塩準安定形結晶の製法に関する。
【0002】
【従来の技術】塩酸セルトラリンは、抗うつ剤として有用な化合物である〔米国特許第4,536,518 号明細書〕。
【0003】従来、粉末X線回折図において、角度2θが、7．1°、12．7°、14．1°、15．3°、15．7°、21．2°、23．4°および26．3°であるときに特徴的な回折ピークを示す塩酸セルトラリン（Form I）は、安定な結晶構造を有するので、医薬などに使用されている〔米国特許第5,248,699 号明細書〕。
【0004】しかしながら、前記結晶構造を有する塩酸セルトラリンは、安定した結晶構造を有することに起因して、溶媒に対する溶解性およびバイオアベイラビリティ（生物学的利用率）が低いおそれがある。
【0005】
【発明が解決しようとする課題】本発明は、前記従来技術に鑑みてなされたものであり、従来の安定した結晶構造を有する塩酸セルトラリン（Form I）とは異なり、各種溶媒に対する溶解性やバイオアベイラビリティが良好であると考えられている準安定形の結晶構造を有する塩酸セルトラリンの製法を提供することを目的とする。
【0006】
【課題を解決するための手段】本発明の要旨は、〔1〕　セルトラリン遊離塩基を溶媒に溶解させるか、またはセルトラリン有機酸塩を溶媒に懸濁させた後、得られた溶液または懸濁液に塩酸または塩化水素を導入することを特徴とする式（Ｉ）：
【0007】
【化2】



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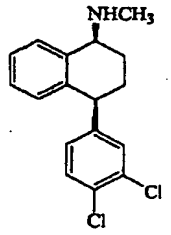
【0008】で表される準安定形塩酸セルトラリン結晶の製法、〔2〕　溶媒が、エステル系有機溶媒、ケトン系有機溶媒またはそれらの混合溶媒である前記〔1〕記載の準安定形塩酸セルトラリン結晶の製法、および
〔3〕　溶液または懸濁液に塩酸または塩化水素を導入する際の温度が、室温～溶媒の還流温度である前記〔1〕または〔2〕記載の準安定形塩酸セルトラリン結晶の製法に関する。
【0009】
【発明の実施の形態】本発明の準安定形塩酸セルトラリン結晶の製法によれば、セルトラリン遊離塩基を溶媒に溶解させるか、またはセルトラリン有機酸塩を溶媒に懸濁させた後、得られた溶液または懸濁液に塩酸または塩化水素を導入することにより、式（Ｉ）：
【0010】
【化3】



・　HCl　　（I）

【0011】で表される準安定形塩酸セルトラリン結晶を製造することができる。
【0012】前記セルトラリン遊離塩基の製法としては、例えば、セルトラリンのマンデル酸塩をアルカリ分解する方法などがあげられる。該セルトラリンのマンデル酸塩は、例えば、（1SR，4SR）－4－（3，4－ジクロロフェニル）－1，2，3，4－テトラヒドロ－N－メチル－1－ナフチルアミンをD－（－）－マンデル酸で光学分割することによって得ることができる。

【００１３】前記セルトラリン有機酸塩の代表例としては、前記セルトラリンのマンデル酸塩などがあげられる。

【００１４】前記溶媒としては、例えば、酢酸エチル、酢酸ブチルなどに代表されるエステル系有機溶媒、アセトン、メチルイソブチルケトンなどに代表されるケトン系有機溶媒、それらの混合溶媒などがあげられる。これらのなかでは、酢酸エチル、酢酸ブチルおよびメチルイソブチルケトンは、本発明において好適に使用しうるものである。

【００１５】前記溶媒の使用量は、セルトラリン遊離塩基またはセルトラリン有機酸塩１００重量部に対して、１００～２００００重量部、好ましくは５００～１００００重量部程度であることが望ましい。セルトラリン遊離塩基を溶媒に溶解させる際の温度は、通常、０～１５０℃程度、好ましくは２０～１２０℃程度であることが望ましい。

【００１６】セルトラリン遊離塩基を有機溶媒に溶解させるか、またはセルトラリン有機酸塩を溶媒に懸濁させた後、得られた溶液または懸濁液に、塩酸または塩化水素ガスを導入することにより、準安定形塩酸セルトラリン結晶を得ることができる。なお、塩酸を用いる場合、前記溶液または懸濁液に塩酸を滴下すればよく、また塩化水素を用いる場合、前記溶液または懸濁液に塩化水素ガスを吹き込めばよい。

【００１７】塩酸または塩化水素の使用量は、セルトラリン遊離塩基またはセルトラリン有機酸塩が塩酸セルトラリンとなるのに十分な量が選ばれる。かかる塩酸または塩化水素の使用量は、通常、セルトラリン遊離塩基またはセルトラリン有機塩基１．０モルに対して、１．０～５．０モル、好ましくは、１．１～３．０モルであることが望ましい。なお、塩酸セルトラリンが生成したことは、例えば、溶液または懸濁液のｐＨが酸性を示すことなどにより、確認することができる。

【００１８】塩酸または塩化水素を溶液または懸濁液に導入する際の溶液または懸濁液の温度は、特に限定されず、室温から溶媒の還流温度であればよい。

【００１９】反応終了後、反応溶液を、例えば、室温に冷却し、析出した結晶を沪過により回収することができる。なお、反応溶液から結晶を析出させる際には、必要により、種晶を接種し、結晶を析出させてもよい。

【００２０】このようにして得られた塩酸セルトラリンの結晶構造は、粉末Ｘ線回折により容易に測定することができる。かかる粉末Ｘ線回折によれば、前記塩酸セルトラリンは、米国特許第5,248,699 号明細書に記載の準安定形結晶である形態II(Form II) を有するものであることがわかる。

【００２１】したがって、前記塩酸セルトラリンは、従来の安定した結晶構造を有する塩酸セルトラリンとは異なり、各種溶媒に対する溶解性やバイオアベイラビリティに優れる可能性を有するという性質を持つ。

【００２２】

【実施例】次に、本発明を実施例に基づいてさらに詳細に説明するが、本発明はかかる実施例のみに限定されるものではない。

【００２３】参考例

撹拌機および温度計を備えた３００ｍｌの三つ口フラスコに、酢酸エチル１２０ｍｌ、水１００ｍｌおよびセルトラリンのＤ－（－）－マンデル酸塩３．０ｇ（６．５４ｍｍｏｌ）を添加し、混合した。

【００２４】次に、フラスコ内に、２５％水酸化ナトリウム水溶液２．１ｇ（１３．１ｍｍｏｌ）を添加し、室温で１時間撹拌した。

【００２５】静置分液後、酢酸エチル層を水５０ｍｌで洗浄し、エバポレーターにて減圧濃縮した。濃縮残渣をイソプロピルアルコール９０ｍｌに溶解させ、塩化水素ガス０．３６ｇ（９．８６ｍｍｏｌ）を吹き込んだ。

【００２６】次に、析出した結晶を沪過し、乾燥し、塩酸セルトラリン結晶１．８４ｇを得た。

【００２７】得られた結晶について、粉末Ｘ線回折を以下の方法にしたがって調べた。その結果を図６に示す。

〔粉末Ｘ線回折〕

粉末Ｘ線回折装置：理学電機（株）製、Mini Flex 〔 CuKα_1 線〕

測定条件：

対陰極：Cu

フィルター：Kβ

管電圧：３０kV

管電流：１５mA

走査速度：２°／min

【００２８】図６に示された結果から、参考例で得られた塩酸セルトラリンは、米国特許第5,248,699 号明細書に記載の安定結晶〔形態Ｉ(Form I)〕を有するものであることがわかる。

【００２９】実施例１

撹拌機および温度計を備えた２００ｍｌの三つ口フラスコに、酢酸エチル１００ｍｌ、水５０ｍｌおよびセルトラリンのＤ－（－）－マンデル酸塩１．５０ｇ（３．２７ｍｍｏｌ）を添加し、混合した。

【００３０】次に、該フラスコ内に、２５％水酸化ナトリウム水溶液１．０ｇ（６．２５ｍｍｏｌ）を添加し、室温で３０分間撹拌した。

【００３１】静置分液後、酢酸エチル層を水５０ｍｌで洗浄し、硫酸マグネシウムにて乾燥した。得られた酢酸エチル層を８０℃に昇温し、塩酸セルトラリンの形態IIの結晶を接種後、塩化水素ガスを吹き込み、約５分間撹拌したところ、白色スラリーが得られた。

【００３２】得られたスラリーを室温に冷却し、沪過し、乾燥し、塩酸セルトラリン結晶０．６５ｇを得た。

【００３３】得られた結晶について、粉末Ｘ線回折を製

造例と同様の方法により調べた。その結果を図1に示す。

【0034】図1に示された結果から、実施例1で得られた塩酸セルトラリンは、米国特許第5,248,699号明細書に記載の準安定形結晶である形態IIの構造を有するものであることがわかる。

【0035】実施例2

撹拌機および温度計を備えた200ml の三つ口フラスコに、酢酸ブチル50ml、水30mlおよびセルトラリンのD-(-)-マンデル酸塩1.50g(3.27mmol)を添加し、混合した。

【0036】次に、フラスコ内に、25%水酸化ナトリウム水溶液1.0g(6.25mmol)を添加し、室温で30分間撹拌した。

【0037】静置分液後、酢酸ブチル層を水30mlで洗浄し、硫酸マグネシウムにて乾燥した。得られた酢酸ブチル層を115℃に昇温し、塩化水素ガスを吹き込み、塩酸セルトラリンの形態IIの結晶を接種したところ、白色スラリーが得られた。

【0038】得られたスラリーを室温に冷却し、沪過し、乾燥し、塩酸セルトラリン結晶0.75gを得た。

【0039】得られた結晶について、粉末X線回折を製造例と同様の方法により調べた。その結果を図2に示す。

【0040】図2に示された結果から、実施例2で得られた塩酸セルトラリン結晶は、準安定形結晶である形態IIの構造を有するものであることがわかる。

【0041】実施例3

撹拌機および温度計を備えた100ml の三つ口フラスコに、酢酸エチル80ml、水50mlおよびセルトラリンのD-(-)-マンデル酸塩1.50g(3.27mmol)を添加し、混合した。

【0042】次に、該フラスコ内に、25%水酸化ナトリウム水溶液1.0g(6.25mmol)を添加し、室温で30分間撹拌した。

【0043】静置分液後、酢酸エチル層を水80mlで洗浄し、エバポレーターにて減圧濃縮した。濃縮残渣にメチルイソブチルケトン50mlを添加し、115℃に昇温し、セルトラリン遊離塩基を溶解させた後、塩化水素ガスを吹き込んだところ、白色スラリーが得られた。

【0044】得られたスラリーを室温に冷却し、沪過し、乾燥し、塩酸セルトラリン結晶1.07gを得た。

【0045】得られた結晶について、粉末X線回折を製造例と同様の方法により調べた。その結果を図3に示す。

【0046】図3に示された結果から、実施例3で得られた塩酸セルトラリン結晶は、準安定形結晶である形態IIの構造を有するものであることがわかる。

【0047】実施例4

実施例3において、溶液還流下、塩化水素ガスを吹き込む代わりに、95℃で35%塩酸0.68g(6.52mmol)を添加し、塩酸セルトラリンの形態IIの結晶を接種した。結晶析出後、室温まで冷却し、沪過、乾燥し、塩酸セルトラリン結晶0.82gを得た。

【0048】得られた結晶について、粉末X線回折を製造例と同様の方法により調べた。その結果を図4に示す。

【0049】図4に示された結果から、実施例4で得られた塩酸セルトラリン結晶は、準安定形結晶である形態IIの構造を有するものであることがわかる。

【0050】実施例5

撹拌機および温度計を備えた100ml の三つ口フラスコに、メチルイソブチルケトン50mlおよびセルトラリンのD-(-)-マンデル酸塩1.50g(3.27mmol)を添加し、90℃で撹拌した。そのスラリー液に35%塩酸1.0g(9.59mmol)を添加し、塩酸セルトラリンの形態IIの結晶を接種し、90℃で30分間撹拌した後、50℃まで冷却し、同温度で沪過、乾燥し、塩酸セルトラリン結晶0.60gを得た。

【0051】得られた結晶について、粉末X線回折を製造例と同様の方法により調べた。その結果を図5に示す。

【0052】図5に示された結果から、実施例5で得られた塩酸セルトラリン結晶は、準安定形結晶である形態IIの構造を有するものであることがわかる。

【0053】

【発明の効果】本発明の製法によれば、医薬品として有用な準安定形の結晶構造を有する塩酸セルトラリン結晶を得ることができるという効果が奏される。

【図面の簡単な説明】

【図1】図1は、本発明の実施例1で得られた準安定形塩酸セルトラリン結晶の粉末X線回折図である。

【図2】図2は、本発明の実施例2で得られた準安定形塩酸セルトラリン結晶の粉末X線回折図である。

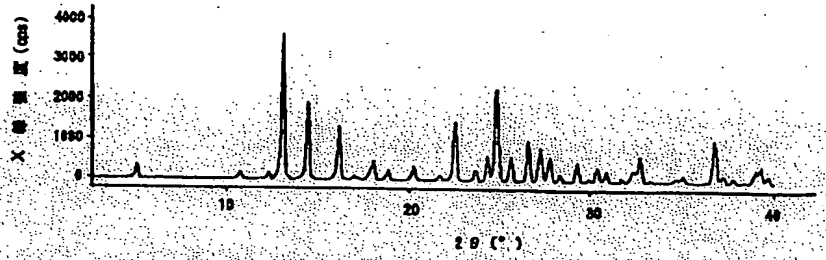
【図3】図3は、本発明の実施例3で得られた準安定形塩酸セルトラリン結晶の粉末X線回折図である。

【図4】図4は、本発明の実施例4で得られた準安定形塩酸セルトラリン結晶の粉末X線回折図である。

【図5】図5は、本発明の実施例5で得られた準安定形塩酸セルトラリン結晶の粉末X線回折図である。

【図6】図6は、参考例で得られた塩酸セルトラリン結晶の粉末X線回折図である。

【図1】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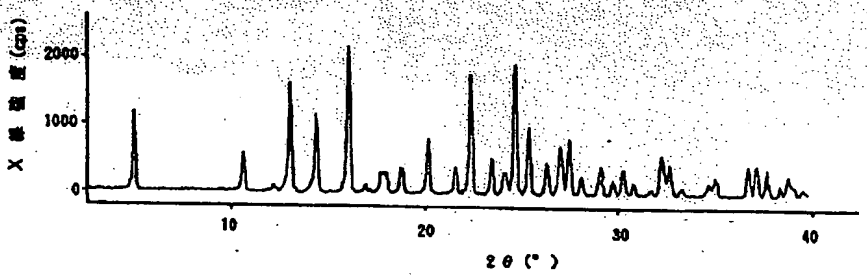
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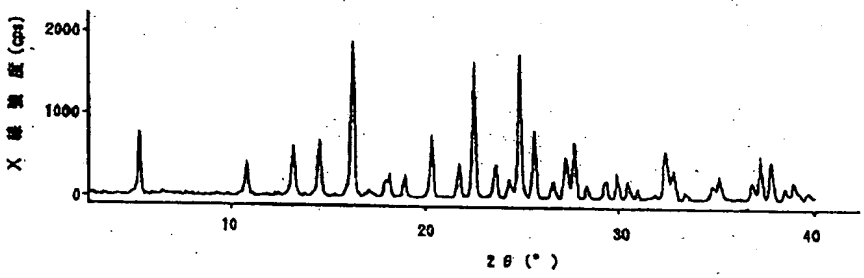
2θ(°)

【図3】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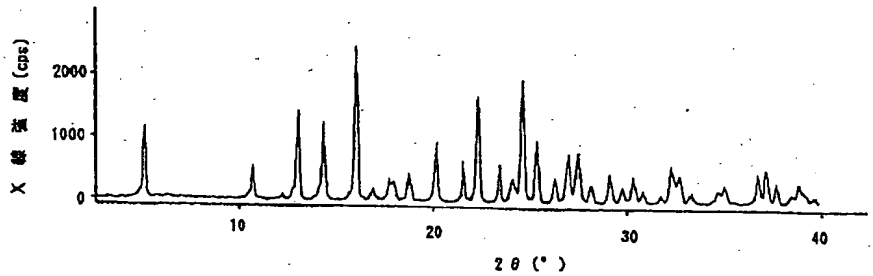
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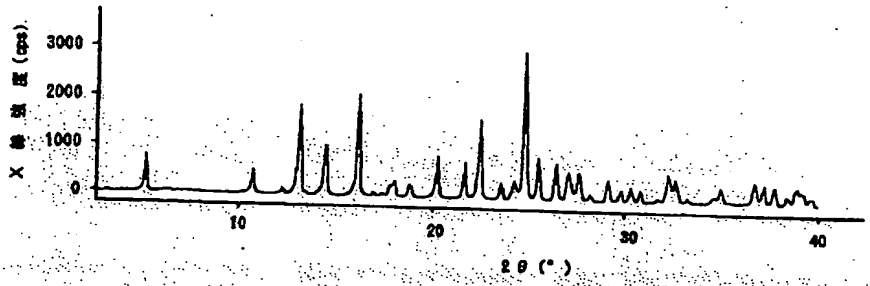
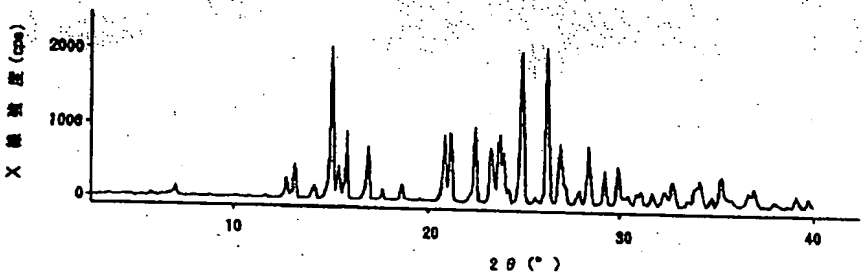


【図6】



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Continued on the last page

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(54) [Title of the invention]

Method for Manufacture of Sertraline Hydrochloride.

(57) [Summary]

[Topic]

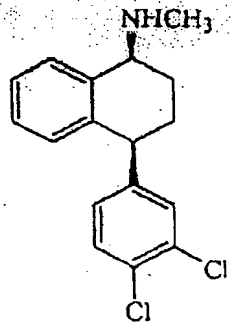
To offer a method for manufacture of sertraline hydrochloride that possesses semi stable crystal structure

that is considered to have satisfactory solubility with respect to different solvents and bio-availability, which is different from sertraline hydrochloride that possesses stabilized crystal structure of the past.

[Method for solution]

The method for manufacture of semi stable type sertraline hydrochloride crystals shown by the general formula (I) given below has the characteristic of either dissolving sertraline freebase in solvent or suspending sertraline organic acid salt in solvent and then, introducing hydrochloric acid or hydrogen chloride in the obtained solution or suspension.

[Formula 1]



· HCl

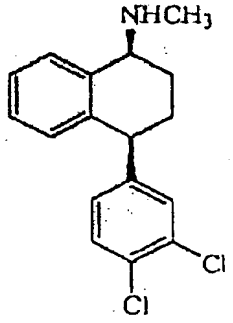
(I)

[Scope of patent claims]

[Claim 1]

The method for manufacture of semi stable type sertraline hydrochloride crystals shown by the general formula (I) given below has the characteristic of either dissolving sertraline freebase in solvent or suspending sertraline organic acid salt in solvent and then, introducing hydrochloric acid or hydrogen chloride in the obtained solution or suspension.

[Formula 1]



· HCl (I)

[Claim 2]

The method for manufacture of semi stable type sertraline

hydrochloride crystals described above in claim number 1 in which solvent is ester group organic solvent, ketone group organic solvent or their mixed solvent.

[Claim 3]

The method for manufacture of semi stable type sertraline hydrochloride crystals described above in claim number 1 or 2 in which temperature at the time of introducing hydrochloric acid or hydrogen chloride in the solution or suspension is within the range from room temperature ~ reflux temperature of solvent.

[Detailed description of the invention]

[0001]

[Technical field of the invention]

The present invention relates to the method for manufacture of semi stable type sertraline hydrochloride crystals. In further details, the present invention relates to the method for manufacture of semi stable type crystals of (1S, 4S) - 4 - (3, 4 - di chloro phenyl) - 1, 2, 3, 4

- tetra hydro - N - methyl - 1 - naphtyl amine hydrochloride salt that is useful as an antidepressant.

[0002]

[Techniques of the past]

Sertraline hydrochloride is useful as antidepressant [refer to American Patent number 4,536,518].

[0003]

The sertraline hydrochloride showing characteristic diffraction peak when 2? is 7.1°, 12.7°, 14.1°, 15.3°, 15.7°, 21.2°, 23.4° and 26.3° in powder X ray diffraction figure, (Form I) is used as medicine since past as it has stable crystal structure (refer to American Patent number 5,248,699).

[0004]

However, sertraline hydrochloride having the crystal structure mentioned above has low solubility with respect to solvent and bio-availability (biological usage ratio) due to its stabilized crystal structure.

[0005]

[Problems the invention solves]

The present invention has been devised in the view of techniques of the past mentioned above and it aims at offering a method for manufacture of sertraline hydrochloride that possesses semi stable type crystal structure that is considered to have satisfactory solubility with respect to different solvents and bio-availability, which is different from sertraline hydrochloride that possesses stabilized crystal structure of the past (Form I).

[0006]

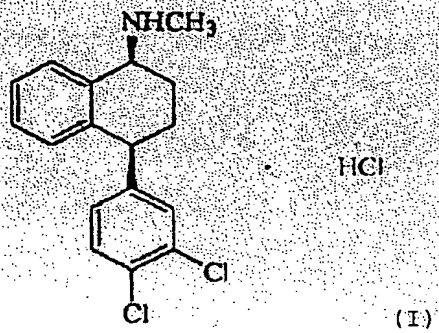
[Method to solve the problems]

The present invention relates to [1] the method for manufacture of semi stable type sertraline hydrochloride crystals shown by the general formula (I) given below that has the characteristic of either dissolving sertraline freebase in solvent or suspending sertraline organic acid

salt in solvent and then, introducing hydrochloric acid or hydrogen chloride in the obtained solution or suspension,

[0007]

[Formula 1]



(I)

[0008]

[2] the method for manufacture of semi stable type sertraline hydrochloride crystals described above in [1] in which solvent is ester group organic solvent, ketone group organic solvent or their mixed solvent, and [3] the method for manufacture of semi stable type sertraline hydrochloride crystals described above in [1] or [2] in which temperature at the time of introducing hydrochloric

acid or hydrogen chloride in the solution or suspension is within the range from room temperature ~ reflux temperature of solvent.

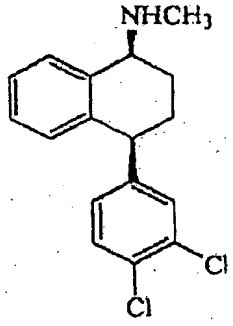
[0009]

[State of practicalization of the invention]

If the method for manufacture of semi stable type sertraline hydrochloride crystals is used, then semi stable type sertraline hydrochloride crystals shown by the general formula (I)

[0010]

[Formula 3]



(I)

[0011]

can be manufactured by either dissolving sertraline freebase in solvent or suspending sertraline organic acid salt in solvent and then, introducing hydrochloric acid or hydrogen chloride in the obtained solution or suspension.

[0012]

As regards the manufacturing method of sertraline freebase mentioned above, the method in which mandelic acid salt of sertraline is subjected to alkali decomposition can be given. The mandelic acid salt of sertraline can be obtained by carrying out optical resolution of (1SR, 4SR) - 4 - (3, 4 - di chloro phenyl) - 1, 2, 3, 4 - tetra hydro - N - methyl - 1 - naphtyl amine by using D - (-) mandelic acid.

[0013]

As regards the representative examples of sertraline organic acid salt mentioned above, mandelic acid salt of sertraline mentioned above can be given.

[0014]

As regards the solvent mentioned above, ester group organic solvent represented by ethyl acetate, butyl acetate etc., ketone group organic solvent represented by acetone, methyl iso butyl ketone etc. or their mixed solvent can be given. Among these also, ethyl acetate, butyl acetate and methyl iso butyl ketone are desired to be used.

[0015]

The quantity with which solvent mentioned above is used, should be within the range from 100 ~ 20000 parts by weight, desirably, within the range from 500 ~ 10000 parts by weight, with respect to 100 parts by weight of sertraline freebase or sertraline organic acid salt. The temperature at the time of dissolving sertraline freebase in solvent should be within the range from 0 ~ 150°C, desirably, within the range from 20 ~ 120°C.

[0016]

The semi stable type sertraline hydrochloride crystals can be obtained by either dissolving sertraline freebase

in organic solvent or suspending sertraline organic acid salt in solvent and then, introducing hydrochloric acid or hydrogen chloride in the obtained solution or suspension. Moreover, in the case of using hydrochloric acid, hydrochloric acid can be dropped in the solution mentioned above and in the case of using hydrogen chloride, hydrogen chloride gas can be blown in the solution or suspension mentioned above.

[0017]

As regards the quantity with which hydrochloric acid or hydrogen chloride is used, quantity that is sufficient to convert sertraline freebase into sertraline hydrochloride is selected. The quantity with which hydrochloric acid or hydrogen chloride mentioned above is used should be within the range from 1.0 ~ 5.0 mole, desirably, 1.1 ~ 3.0 mole with respect to 1.0 mole of sertraline freebase or sertraline organic acid salt. Moreover, generation of sertraline hydrochloride can be confirmed by indicating that pH of

solution is acidic.

[0018]

There is no particular restriction over the temperature of solution at the time of introducing hydrochloric acid or hydrogen chloride to the solution or suspension and it can be within the range from room temperature - reflux temperature of solvent.

[0019]

After the completion of reaction, reaction solution is cooled to room temperature based on which deposited crystals can be recovered by filtration. Moreover, at the time of depositing crystals from reaction solution, crystals can be deposited by bringing the solution into contact with seed crystals as per requirement.

[0020]

The crystal structure of sertraline hydrochloride thus obtained can be easily measured by powder X ray diffraction. It can be understood from powder X ray diffraction mentioned

above, that it possesses state II (Form II) that is semi stable type crystals mentioned in American Patent number 5,248,699.

[0021]

Therefore, sertraline hydrochloride mentioned above is different from sertraline hydrochloride that possesses stable crystal structure of the past, and it possesses characteristic of possibly having excellent solubility with respect to different solvents and bio-availability.

[0022]

[Practical examples]

The present invention has been explained below in further details with the help of practical examples. However, the present invention is not restricted only to these practical examples.

[0023]

Reference example

120 ml of ethyl acetate, 100 ml of water and 3.0 g (6.54

mmol) of D - (-) - mandelic acid salt of sertraline were taken in 300 ml flask having 3 openings and equipped with a stirrer and thermometer, and were mixed.

[0024]

Next, 2.1 g (13.1 mmol) of 25 % aqueous solution of sodium hydroxide was added to the flask mentioned above after which it was stirred at room temperature for 1 hour.

[0025]

After that, the obtained solution was subjected to liquid separation by keeping it undisturbed after which ethyl acetate layer was washed with 50 ml of water and was concentrated under reduced pressure in an evaporator. The concentrated residue was dissolved in 90 ml of iso propyl alcohol and 0.36 g (9.86 mmol) of hydrogen chloride gas was blown in it.

[0026]

Next, the deposited crystals were filtered and dried when 1.84 g of sertraline hydrochloride crystals were obtained.

[0027]

The obtained crystals were analyzed by powder X ray diffraction by the following method. The results have been presented in figure 6 given below.

[Powder X ray diffraction]

Powder X ray diffraction device: Rigaku Denki (Rigaku Electrical Machines) make, Mini Flex [CuK? $_1$ rays]

Measurement Conditions:

Counter cathode: Cu

Filter: K?

Tube voltage: 30 kV

Tube current: 15 mA

Scanning rate: 2^0/min

[0028]

It can be understood from the results shown in figure 6 that sertraline hydrochloride obtained in reference example possesses stable crystals [state I (Form I) described in American Patent number 5,248,699.

[0029]

Practical example 1

100 ml of ethyl acetate, 50 ml of water and 1.5 g (3.27 mmol) of D - (-) - mandelic acid salt of sertraline were taken in 200 ml flask having 3 openings and equipped with a stirrer and thermometer, and were mixed.

[0030]

Next, 1.0 g (6.25 mmol) of 25 % aqueous solution of sodium hydroxide was added to the flask mentioned above after which it was stirred at room temperature for 30 minutes.

[0031]

After that, the obtained solution was subjected to liquid separation by keeping it undisturbed after which ethyl acetate layer was washed with 50 ml of water and was dried using magnesium sulfate. The obtained ethyl acetate layer was heated at 80°C and crystals of state II of sertraline hydrochloride were brought into contact with seed after which hydrogen chloride gas was blown and it was stirred

for approximately 5 minutes when white slurry was obtained.

[0032]

The obtained slurry was cooled to room temperature and it was filtered and dried when 0.65 g of sertraline hydrochloride crystals were obtained.

[0033]

The obtained crystals were analyzed by powder X ray diffraction by the method same as that used in reference example. The results have been presented in figure 1 given below.

[0034]

It can be understood from the results shown in figure 1 that sertraline hydrochloride obtained in practical example 1 possesses structure of state II that is semi stable type crystals described in American Patent number 5,248,699.

[0035]

Practical example 2

50 ml of butyl acetate, 30 ml of water and 1.50 g (3.27 mmol) of D - (-) - mandelic acid salt of sertraline were taken in 200 ml flask having 3 openings and equipped with a stirrer and thermometer, and were mixed.

[0036]

Next, 1.0 g (6.25 mmol) of 25 % aqueous solution of sodium hydroxide was added to the flask mentioned above after which it was stirred at room temperature for 30 minutes.

[0037]

After that, the obtained solution was subjected to liquid separation by keeping it undisturbed after which butyl acetate layer was washed with 30 ml of water and was dried using magnesium sulfate. The obtained butyl acetate layer was heated at 115°C and hydrogen chloride gas was blown after which crystals of state II of sertraline hydrochloride were brought into contact with seed when white slurry was obtained.

[0038]

The obtained slurry was cooled to room temperature and it was filtered and dried when 0.75 g of sertraline hydrochloride crystals were obtained.

[0039]

The obtained crystals were analyzed by powder X ray diffraction by the method same as that used in reference example. The results have been presented in figure 2 given below.

[0040]

It can be understood from the results shown in figure 2 that sertraline hydrochloride obtained in practical example 2 possesses structure of state II that is semi stable type crystals.

[0041]

Practical example 3

80 ml of ethyl acetate, 50 ml of water and 1.50 g (3.27 mmol) of D - (-) - mandelic acid salt of sertraline were taken in 100 ml flask having 3 openings and equipped with

a stirrer and thermometer, and were mixed.

[0042]

Next, 1.0 g (6.25 mmol) of 25 % aqueous solution of sodium hydroxide was added to the flask mentioned above after which it was stirred at room temperature for 30 minutes.

[0043]

After that, the obtained solution was subjected to liquid separation by keeping it undisturbed after which ethyl acetate layer was washed with 80 ml of water and was concentrated under reduced pressure in an evaporator. 50 ml of methyl iso butyl ketone was added to the concentrated residue and it was heated to 115°C based on which sertraline freebase was dissolved after which hydrogen chloride gas was blown when white slurry was obtained.

[0044]

The obtained slurry was cooled to room temperature and it was filtered and dried when 1.07 g of sertraline hydrochloride crystals were obtained.

[0045]

The obtained crystals were analyzed by powder X ray diffraction by the method same as that used in reference example. The results have been presented in figure 3 given below.

[0046]

It can be understood from the results shown in figure 3 that sertraline hydrochloride obtained in practical example 3 possesses structure of state II that is semi stable type crystals.

[0047]

Practical example 4

In practical example 3, 0.68 g (6.52 mmol) of 35 % hydrochloric acid was added at 95°C instead of blowing hydrogen chloride gas under solution reflux and crystals of state II of sertraline hydrochloride were brought into contact with seeds. After crystal deposition, it was cooled up to room temperature and was filtered and dried when 0.82

g of sertraline hydrochloride crystals were obtained.

[0048]

The obtained crystals were analyzed by powder X ray diffraction by the method same as that used in reference example. The results have been presented in figure 4 given below.

[0049]

It can be understood from the results shown in figure 4 that sertraline hydrochloride obtained in practical example 4 possesses structure of state II that is semi stable type crystals.

[0050]

Practical example 5

50 ml of methyl iso butyl ketone and 1.50 g (3.27 mmol) of D – (-) - mandelic acid salt of sertraline were taken in 100 ml flask having 3 openings and equipped with a stirrer and thermometer, and these were stirred at 90°C. 1.0 g (9.59 mmol) of 35 % hydrochloric acid was added to this slurry

liquid and crystals of state II of sertraline hydrochloride were brought into contact with seed and then, it was stirred at 90°C for 30 minutes after which it was cooled up to 50°C and it was filtered and dried at the same temperature when 0.60 g of sertraline hydrochloride crystals were obtained.

[0051]

The obtained crystals were analyzed by powder X ray diffraction by the method same as that used in reference example. The results have been presented in figure 5 given below.

[0052]

It can be understood from the results shown in figure 5 that sertraline hydrochloride obtained in practical example 5 possesses structure of state II that is semi stable type crystals.

[0053]

[Effect / result of the invention]

If the manufacturing method of the present invention is

used, then sertraline hydrochloride crystals having semi stable type crystal structure, that is useful as a medicine can be obtained.

[Brief explanation of figures]

[Figure 1]

Powder X ray diffraction figure of semi stable type sertraline hydrochloride obtained in practical example 1 of the present invention.

[Figure 2]

Powder X ray diffraction figure of semi stable type sertraline hydrochloride obtained in practical example 2 of the present invention.

[Figure 3]

Powder X ray diffraction figure of semi stable type sertraline hydrochloride obtained in practical example 3 of the present invention.

[Figure 4]

Powder X ray diffraction figure of semi stable type

sertraline hydrochloride obtained in practical example 4 of the present invention.

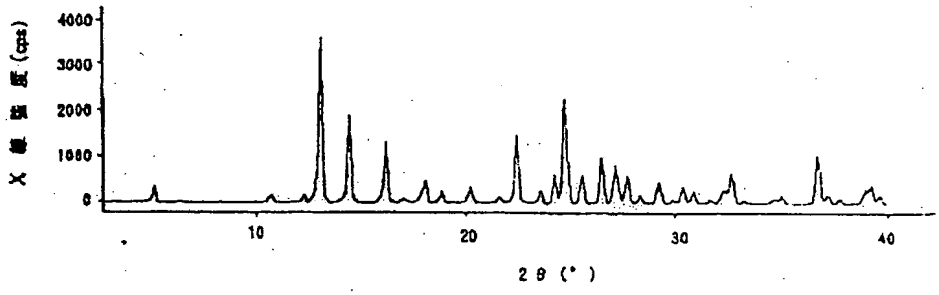
[Figure 5]

Powder X ray diffraction figure of semi stable type sertraline hydrochloride obtained in practical example 5 of the present invention.

[Figure 6]

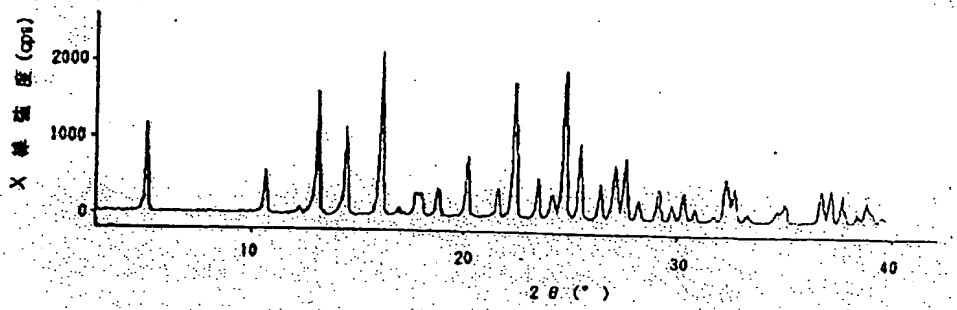
Powder X ray diffraction figure of semi stable type sertraline hydrochloride obtained in reference example.

[Figure 1]



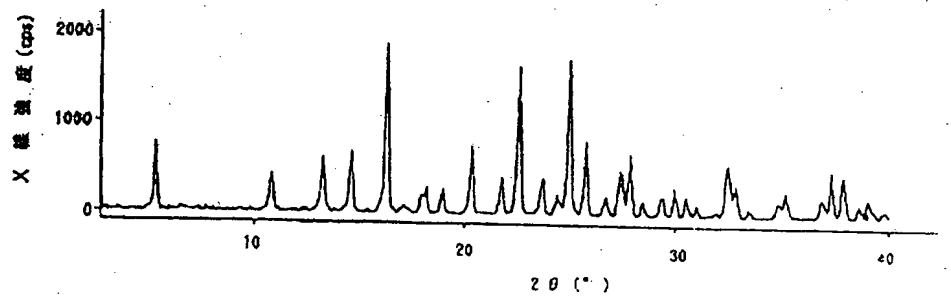
(Japanese characters in the above figure means X ray intensity (cps))

[Figure 2]



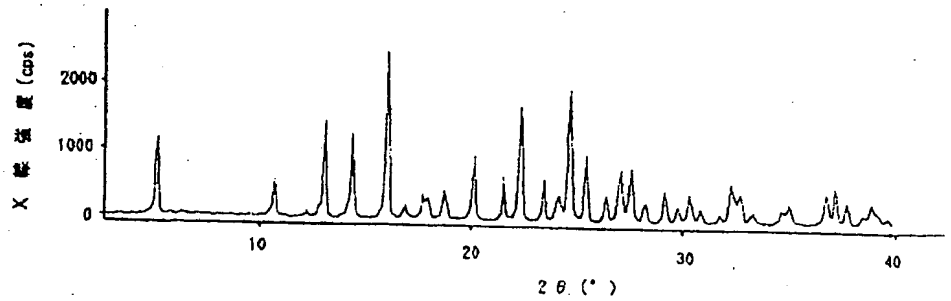
(Japanese characters in the above figure means X ray intensity (cps))

[Figure 3]



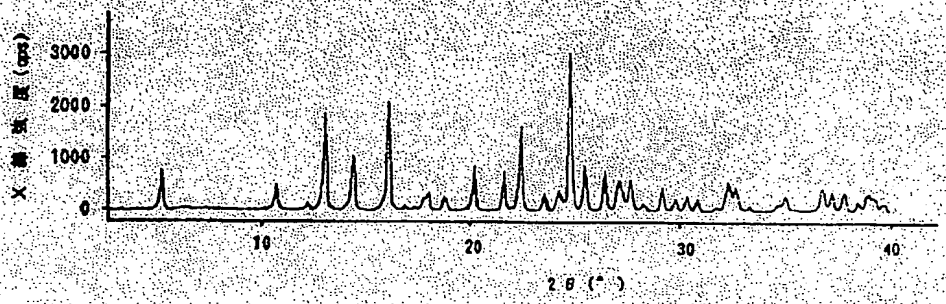
(Japanese characters in the above figure means X ray intensity (cps))

[Figure 4]



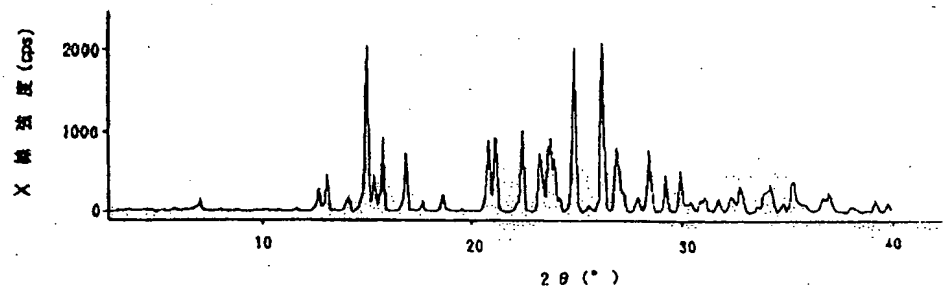
(Japanese characters in the above figure means X ray intensity (cps))

[Figure 5]



(Japanese characters in the above figure means X ray intensity (cps))

[Figure 6]



(Japanese characters in the above figure means X ray intensity (cps))

Continued from front page

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(Internal to

Comprehensive

Research Center of

Sumika Fine Chem Co.

Ltd.)

F Theme (reference)

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AC90 AD15 …

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